REMARKS/ARGUMENTS

Claims 36 to 49 are pending in the present application. Claim 46 has been amended to specifically recite that the claimed methods inhibit the activity of a core 2 GlcNAc transferase and thereby inhibit synthesis of a core2 oligosaccharide. Support for the claims is replete throughout the specification. All the claims stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking written description and enablement. These rejections are respectfully traversed as explained below.

The Present Invention

The target enzyme of the present invention, core 2 GlcNAc transferase (E.C. 2.4.102) is involved in the early steps of the biosynthesis of core 2 *O*-glycans in a variety of cells including inflammatory cells (*e.g.*, neutrophils) and lymphocytes (*see* Specification page 4, lines 19-27). In many cells, core 2 *O*-glycans comprise the oligosaccharide ligand (sialyl Lewis^X) recognized by the selectin family of leukocyte adhesion molecules (*see* Specification page 4, lines 2-10 and Figure 1). Selectin receptors are known to be associated with a number of functions including leukocyte extravasation at cites of inflammation and lymphocyte trafficking in lymph nodes (*see* Specification page 4, lines 28-29).

Since sialyl Lewis^X is involved in inflammation, lymphocyte trafficking, and other processes, it has been difficult to develop treatments that are effective against chronic inflammation but do not otherwise compromise the body's immune system. The present invention is based on the surprising discovery that by specifically targeting the core 2 GlcNAc transferase (C2 GlcNAcT), extravasation of neutrphils and other inflammatory cells is inhibited, while leaving lymphocyte trafficking and other immune functions relatively intact (*see* Specification page 18, lines 6-11). As explained in the specification, the inventors hypothesize that it is possible that lymphocyte glycoproteins other than those modified by C2 GlcNAcT participate in lymphocyte homing (*see* Specification page 50, lines 2-17).

Thus, based on this discovery those of skill can now treat inflammatory responses by specifically inhibiting the activity C2 GlcNAcT using known methods. The invention is thus

not the discovery of particular inhibitors of C2 GlcNAcT, but the discovery that the enzyme is particularly useful target in the treatment of inflammation.

Written Description

The rejection is based on an allegation that the specification fails to provide adequate description for the distinguishing features of shared by members of the genus of compounds that inhibit activity of C2 GlcNAcT. As noted by the Examiner, the specification teaches that inhibitors of the invention can include immunoglobulins, suicide substrates, alkylating agents, and substrate analogs. The Examiner's position appears to be that in the absence of common structural features shared by all of these inhibitors, the claims lack written description.

The written description requirement is satisfied when the specification describes the claimed invention in sufficient detail that one of skill in the art can reasonably conclude that the inventor had possession of the claimed invention (*see, e.g.*, MPEP § 2163(I), citing *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991).

According to the Federal Circuit, Applicants have some flexibility in the "mode selected for compliance" with the written description requirement. *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886, 1896 (Fed. Cir. 2004). In *Rochester*, the Federal Circuit cited *In re Herschler*, where the CCPA found that "claims drawn to the use of known chemical compounds in a manner auxiliary to the invention must have a corresponding written description ***only so specific as to lead one having ordinary skill in the art to that class of compounds***." *In re Herschler*, 200 USPQ 711, 718 (CCPA, 1979) (emphasis added). Moreover, it is well settled that the description need only describe in detail that which is new or not conventional. *See Hybritech v. Monoclonal Antibodies,* 231 USPQ 81, 94 (Fed. Cir. 1986); M.P.E.P. 2163.

The Examiner's rejection appears to be largely based on a concern that the C2 GlcNAcT inhibitors used in the methods of the invention are defined primarily by their function. There is, however, no ban on functional language to define an essential element of an invention. See *In re Feutterer*, 319 F.2d 259, 264, 138 USPQ 217, 2211 (citing *General Electric v. Wabash Applicance Corp. et al.*, 304 U.S. 364; 37 USPQ 466).

The Federal Circuit has made it clear that this is true even for compounds as complex as genetic materials: "It is not correct . . . that all functional descriptions of genetic material fail to meet the written description requirement." See *Enzo Biochem Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 1324, 63USPQ2d 1609, 1613 (Fed. Cir. 2002). See also *Moba B.V. v. Diamond Automation Inc.*, 325 F.3d 1306, 1320, 66 USPQ2d 1429, 1439 (CA FC 2003) (stating "[m]ore recently, in *Enzo Biochem*, we clarified that *Eli Lilly* did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, ***the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure.*** *Amgen*, 314 F.3d at 1332") (emphasis added).

This case law is consistent with the MPEP instructions with regard to the written description requirement:

> Whether the specification shows that applicant was in possession of the claimed invention is not a single, simple determination, but rather is a factual determination reached by considering a number of factors. Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. ***Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient.***
> (MPEP §2163, page 2100-167, Eighth Edition, February 2003 Revision, Emphasis added).

Here, the Examiner is apparently requiring that ***all*** inhibitors comprise a common structural feature to meet the written description requirement. The Examiner notes that inhibitors useful in the invention could include immunoglobulins, suicide substrates, alkylating agents, and substrate analogs. As noted in the office action, applicants provide teaching relating to sugar nucleotides, nucleotides, and acceptor substrate analogs. Clearly, the structure of the particular inhibitor will depend upon the strategy used to inhibit the C2 GlcNAcT. To base patentability

upon the identification of a common structural feature is clearly improper and not contemplated by the patent laws.

While there may be no common structural feature to all inhibitors useful in the invention, particular classes of inhibitors noted in the office action share common structural features. The disclosed inhibitory function is thus clearly correlated to a particular, known structure.

For example, in the case of inhibitors based on sugar nucleotides, the donor substrate for C2 GlcNAcT is known to be UDP-GlcNAc (*see* Specification, page 20, line 30). Using this knowledge, one of skill in the art can readily synthesize a number of sugar nucleotides. For instance, as explained in the Specification at page 21, lines 9-20, both the ester linkage between the sugar and phosphate and the anhydride linkage of the pyrophosphate are potential targets of enzymatic cleavage. Replacement of the O-P or C-O linkage with a more stable C-P bond provides nucleotide monophosphate or diphosphate sugar analogs that are more resistant to enzymatic degradation. Such compounds have been described in the prior art. *See, e.g.,* Vaghefi *et al., J. Med. Chem.* 30:1383-1391 (1987), and Vaghefi *et al., J. Med. Chem.* 30:1391-1399 (1987). Another approach is to replace the monophosphate or diphosphate bridge between the sugar residue and the nucleoside moiety. For instance, the diphosphate bridge can be replaced with an isosteric -OCONHSO$_2$O- residue. *See*, Samarasa, *et al., J. Med. Chem.* 28:40-46 (1985). Indeed, as explained at page 21, lines 21-30, analogs of sugar nucleotides capable of inhibiting glycosylation have been used as antibiotics and antiviral agents.

In light of the wealth of information about the structure of this class of inhibitory compound, applicants respectfully submit that the disclosed function is clearly correlated to a particular, known structure.

The same correlation between structure and function is known for nucleotides, which, as explained at page 22, lines 3-6, have been found to inhibit glycosyltransferases. As specifically noted UDP and UMP can be used to inhibit C2 GlcNAcT.

Acceptor substrates are another class of inhibitor that share common structural features that are correlated with the inhibitory function. As explained in detail in the

specification, and shown in Figure 1, the acceptor substrate for C2 GlcNAcT is Galβ1,3GalNAc. Again, the common structural features correlated with the desired function is well known. Making and using analogs of acceptor substrates of glycosyltransferases is also well known. As explained at page 22, lines 14-17, one such analog is one in which the galactose residue is replaced by 6-deoxygalactose. The deoxygalactose-containing compounds bind to the C2 GlcNAc-T, but do not function as an acceptor. As explained in detail below, a C2 GlcNAcT inhibitor based on this approach was described in a prior art reference. Surprisingly, the Examiner relies on this reference (Hindsgaul *et al.*) to allege that the present invention lacks enablement.

In light of the above , applicants respectfully submit that the Examiner has failed to establish that the written description is not met. The rejection is clearly improper to the extent it is based on a requirement that ***all*** inhibitors used in the present invention share common structural features. In addition, for different classes of inhibitors, applicants have shown that the disclosed function is sufficiently correlated to a particular, known structure. Finally, a specific inhibitor of GlcNAcT was known at the time of the invention. Withdrawal of the rejection is respectfully requested.

Enablement

The claims also stand rejected for lacking enablement because it would allegedly require undue experimentation to practice the claimed invention. The Examiner acknowledges that in transgenic mice lacking C2 GlcNAcT function, inflammatory responses are inhibited. Thus, the Examiner apparently recognizes that inhibition of this enzyme provides a desirable effect. The basis of the rejection appears, instead, to be that undue experimentation would be required to identify inhibitors that would mimic the effect found in the transgenic mice.

As noted above, the present invention is ***not*** the discovery of C2 GlcNacT inhibitors. Instead, the invention is the discovery that agents that have this function can be used in methods to inhibit inflammatory responses and still maintain immune system function. This

separation of inflammatory cell function and lymphocyte function had not been previously described.

In light of these observations, the inventors recognized that inhibition of C2 GlcNAcT would have therapeutic benefits. Since glycosyltransferases are well studied and many inhibitors of these enzymes are known, the inventors recognized that any of a number of means of inhibiting the activity of glycosyltransferases could be used in the invention. Indeed, as noted above, the specification provides a thorough discussion of inhibitors of glycosyltransferases useful in the methods of the invention. In addition, methods suitable for screening for inhibitors are disclosed on pages 27-31.

A review of the case law reveals that there are situations in which an applicant can properly obtain method claims directed to medical treatments based on the administration of a chemical agent that is defined solely by function and not structure. Indeed, it is well settled that a specification may contain a written description of a broadly claimed invention without describing all species within the scope of the claim. *Utter v. Hiraga* 6 USPQ2d 1709 (Fed. Cir. 1988).

Functional language is proper for non-inventive aspects of the invention

Since the invention is not the discovery of inhibitors, but their use in new therapeutic methods, identification of the inhibitors by their function is entirely proper. The courts have specifically held that rejection of composition claims under §112, first paragraph are improper when the functional language is not used to describe the point of novelty. *See, e.g., In re Fuetterer*, 132 USPQ 217 (CCPA 1963). In *Fuetterer*, the invention was a rubber stock composition useful in producing tire treads. The claims included a recitation of "an inorganic salt capable" of maintaining a homogeneous distribution of another component in the composition. The disclosure listed the function desired and identified four members of the class of inorganic salts having that function. In holding that the description requirement was satisfied the court focused on the fact that the invention claimed was the combination, not the fact that certain salts have colloid suspending properties. The court went on to state:

> The invention description clearly indicates that any inorganic salt which has such properties is usable in his combination. If others in the future discover what inorganic salts additional to those enumerated do have such properties, it is clear appellant will have no control over them *per se*, and equally clear his claims should not be so restricted that they can be avoided merely by using some inorganic salt not named by the appellant in his disclosure. Id. at 223. (emphasis added)

Like the inorganic salts of *Fuetterer*, the inhibitors recited in the claimed methods are defined by their ability to carry out a particular function (inhibit the activity of a certain class of enzymes), not their chemical structure. The particular structure of the inhibitor used is not critical to the invention so long as the desired function is achieved. The ruling in *Fuetterer* makes clear that inhibitors not specifically disclosed in the present application are properly within the scope of the applicants contribution to the art.

A second CCPA decision (*In re Herschler* 200 USPQ 711 (CCPA 1979)) is even more on point. That case dealt with method claims to the use of dimethyl sulfoxide (DMSO) to enhance tissue penetration of physiologically active steroidal agents. The claims were directed to the delivery of all physiologically actives steroids while the great grandparent specification which was relied on for support provided only a single example demonstrating the efficacy of the claimed methods.

Based on the record before them, the court concluded that one of skill would have expected other steroids to function equally well in the claimed methods because steroids, when considered as a class of chemicals delivered using DMSO, should behave quite similarly. The court, therefore, reversed the Patent Office's rejection of these claims reasoning that, because the invention was not the discovery of novel steroidal agents but the delivery of the agents in combination with DMSO, the demonstration of the efficacy of the invention with a number of steroidal agents was not required under §112, first paragraph.

Similarly, in the present case, the claimed invention is not the discovery of a particular C2 GlcNAcT inhibitors but the discovery of a new method of using them to treat

disease. The Examiner has provided nothing to show that one of skill would doubt that a wide range of inhibitors would be useful in the claimed methods. Based on the holding in *Herschler*, it is clear that Appellant need not provide working examples using all inhibitors useful in the claimed methods.

Undue Experimentation is not required to identify inhibitors useful in the invention

The Court of Appeals for the Federal Circuit has long recognized that in a rejection for undue experimentation that: "the key word is 'undue', not 'experimentation'". *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). This decision makes clear that a considerable amount of experimentation is permissible if it is merely routine, or if the specification provides a reasonable amount of guidance respect to the direction in which the experimentation should proceed. The MPEP reiterates this same conclusion (*see*, MPEP § 2164.06).

In an attempt to support the assertion that undue experimentation would be required, the Examiner cites Hindsgaul *et al.* and Jain *et al.* as illustrating the state of the art of glycosyltransferase inhibitors at the time of the invention. As explained below, neither reference supports the examiner's position. Indeed, Hindsgaul *et al.* actually supports applicants position that the state of the art in making and testing glycosyltransferase inhibitors was advanced at the time of the invention.

Hindsgaul *et al.* prepared acceptor analogs for 8 different glycosyltransferases, including C2 GlcNAcT (enzyme G in Table 1 on page 17861). The acceptor analogs were made by replacing the hydroxyl group involved in the glycosylation reaction with hydrogen.[1] As shown in Table 1, the inhibitors worked well for four of the enzymes, including C2 GlcNAcT. The other four did not work. The Examiner apparently takes this as evidence that acceptor analog inhibitors are unpredictable. The authors note, however, that these inhibitors probably did not work because the hydroxyl group is involved in binding to the enzyme, itself. The authors then suggest that this knowledge can be used to design inhibitors that irreversibly bind covalently to the enzyme (*see* page 17862, last paragraph).

[1] As noted above, this analog was specifically disclosed in the specification at page 22, lines 14-17.

Thus, rather than showing the alleged unpredictability of designing glycosyltransferase inhibitors, the Hindsgaul *et al.* paper shows that acceptor analogs ***were*** used to inhibit these enzymes using an approach known at the time of the invention. Indeed, the authors developed acceptor analog that inhibited the target enzyme of the present invention, C2 GlcNAcT. To the extent the Examiner relies on the "failure" of the inhibitors of the other enzymes, it must be kept in mind that the authors provided a useful alternative strategy, based on their results. This publication simply cannot be used to support an assertion that the art was so unpredictable and uncertain that those of skill could not design and test a number of inhibitors useful in the present invention.

In the Office Action, the Examiner also refers to comments the authors make with regard to the relative lack of specificity of sugar nucleotide analogs, which, of course, is not the focus of their paper. The alleged lack of specificity does not address whether such inhibitors would work in inhibiting an inflammatory response. Rather, lack of specificity would be relevant to alleged side effects of administering such inhibitors. The fact that this class of inhibitor may have side effects resulting from a relative lack of specificity is not relevant to the patentability of the claimed methods. It is well settled that it is improper for Office personnel to request evidence of safety in the treatment of humans, or regarding the degree of effectiveness MPEP § 2107.03 V citing *In re Sichert*, 566 F.2d 1154, 196 USPQ 209 (CCPA 1977); *In re Hartop*, 311 F.2d 249, 135 USPQ 419 (CCPA 1962); *In re Anthony*, 414 F.2d 1383, 162 USPQ 594 (CCPA 1969); *In re Watson*, 517 F.2d 465, 186 USPQ 11 (CCPA 1975); *In re Krimmel*, 292 F.2d 948, 130 USPQ 215 (CCPA 1961); *Ex parte Jovanovics*, 211 USPQ 907 (Bd. Pat. App. & Inter. 1981).

The second reference relied on by the Examiner, Jain *et al.*, does not even relate to inhibitors useful in the present invention. This paper deals with analogs of the selectin ligand (sialyl Lewis^X), which compete for binding to selectin receptors with the sialyl Lewis^X structure on the surface of various leukocytes. The compounds cannot act as acceptor analogs of C2 GlcNAcT. As shown in Figure 1, C2 GlcNAcT is involved in making the linkage between

GlcNAc and the GalNAc linked to the protein, not the sialyl Lewis^X structure at the distal end of the glycan. Thus, compounds disclosed by Jain *et al.* cannot act as inhibitors of C2 GlcNAcT as claimed here.

In the present case, an assertion of undue experimentation must be supported by an explanation as to why, in light of the state of the art described above, the assays known in the art or described in the specification could not be used in a routine screen to identify inhibitors of C2 GlcNAcT activity. As noted above, Hindsgaul *et al.* shows that inhibitors ***were*** prepared and tested in the prior art. Clearly, this reference describes suitable assays for testing a wide variety of inhibitors. The present application also discusses suitable assays on pages 27 and 31. In addition, a particular assay is set forth on page 41 of the present application.

In conclusion, the rejection for alleged lack of enablement is improper and should be withdrawn. The functional description of an element of a claim that is not related to the inventive aspect of the invention is entirely proper. Here, the invention is not the discovery of C2 GlcNAcT inhibitors, but the discovery that inhibition of this enzyme is useful in inhibiting inflammatory responses. Thus, the claims need not identify the inhibitors by structure, only by function. Finally, identification of non-exemplified inhibitors is entirely routine in light of the state of the art and standard assays known at the time of the invention.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,

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